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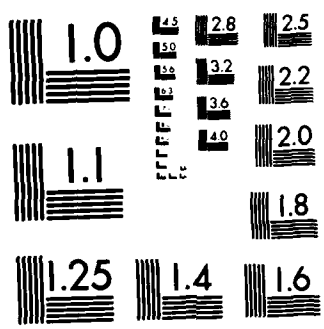

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circadian temperature rhythm, medial preoptic lesions, suprachiasmatic nuclei, hypothalamic damage

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

We have been investigating the hypothalamic control of the generation and maintenance of the circadian temperature rhythm (CTR). Using implanted telemetry devices and automatic drinking measures, we monitored the rhythms of body temperature and drinking in rats before and after various types of hypothalamic damage. When we divided the CTR up into five components--phase, amplitude, limits, precision and period--we found that each component could be affected independent of the others. For instance, after lesions of the suprachiasmatic nuclei, the putative "master clock" in the brain, the phase was

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20. Abstract

altered so that highest body temperature occurred several hours earlier than it did in normals. The amplitude of the CTR was attenuated in most, but not all lesioned rats, and the limits were lower than normal but shorter than 24 hrs, and the precision of the rhythms (when hourly body temperature rose above the daily mean body temperature) was not as regular. In rats with lesions of the medial preoptic area, the phase and period were normal, but the amplitude of the CTR was greatly exaggerated, as were the limits and the daily mean.

In other studies we have shown that the amount of REM sleep is highly dependent on the ambient temperature. After basal forebrain (medial preoptic) lesions, rats that showed no REM sleep at one ambient temperature showed normal amounts at another on the same day.

In a third series of studies, we showed that infant rabbits that were malnourished or cold did not develop a fever after a pyrogen injection when they were left in a warm incubator. (All normal pups did). However, when the pups were allowed to thermoregulate behaviorally by moving in a thermally-graded alleyway, they all chose to rest at higher gradient temperatures than did saline-injected controls and they gave themselves fevers behaviorally.

Summary of Results

THE EFFECT OF LESIONS IN THE PREOPTIC/ANTERIOR HYPOTHALAMUS ON THE REFLEXIVE RESPONSES OF RATS TO COLD STRESS

Final Report

Evelyn Satinoff

July 15, 1984

For the last several years my laboratory has been concerned with elucidating the hypothalamic mechanisms of the circadian temperature rhythm (CTR) in rats. Using computer-controlled temperature telemetry devices implanted into the rats' peritoneal cavity, we have been measuring the CTR of unrestrained, unhandled rats for over a year at a time for individual animals. We have found that the normal amplitude of the CTR in male rats in our laboratory is 2°C (between 36 and 38°C). For several weeks after large lesions in the preoptic area of the hypothalamus, body temperature cycled from as low as 29°C to as high as 41°C in a single day. With recovery, or in rats with smaller lesions, peak-to-trough body temperature amplitudes decreased, ranging between 3 and 5°C for many months, with normal or slightly raised troughs in the light part and grossly higher peaks in the dark part of a 12:12 light-dark cycle. Rats in whom some periventricular tissue was spared had normal body temperature amplitudes but the whole curve was displaced 0.5-1°C above control values. These effects persisted in constant darkness: the range of the free-running period of the lesioned rats was the same as normals, slightly longer than 24 hours. We conclude that in the weeks after medial preoptic lesions thermoregulatory responses are not activated until body temperature is abnormally high or low. As recovery progresses, or if the lesions are smaller to begin with, there may be an imbalance between heat loss and heat production systems so that heat production mechanisms are either always dominant or overshoot when activated. One major function of the preoptic area may be to regulate the upper limit of body temperature.

Another important locus in the control of circadian rhythms are the suprachiasmatic nuclei (SCN). Lesions of these nuclei abolish a variety of rhythms but their effects on body temperature are unclear. Some studies report that SCN lesions abolish the CTR although it can be reinstated and synchronized to a food schedule. Others report that the CTR is unchanged after SCN lesions, and still others that the amplitude and phase of the CTR are altered.

For the last three years we have been measuring temperature and drinking rhythms in rats with SCN lesions. We find that lesions that completely disrupt drinking rhythms, such that water drinking is arrhythmic until the rats are sacrificed, initially disrupt the CTR, but that it returns with an altered phase and amplitude. In constant dark, the CTR free-runs with a rhythm slightly shorter than 24 hours. (Almost all normal rats have free-running body temperature rhythms that have periods slightly longer than 24 hours. These results indicate that there are at least two neural oscillators in the brain of rats, and that the one responsible for generating the body temperature rhythm is located outside of the SCN.

In another series of experiments dealing with the relationship between temperature regulation and sleep, we determined the amounts of sleep and waking in rats at ambient temperatures of 20, 25 and 30°C before and after lesions of the medial preoptic area (the basal forebrain). Rats were hyposomniac at all ambient temperatures for 1-2 days postlesion. After that, sleep was highly ambient temperature-dependent. Rats were typically hyperthermic after complete ablation of the medial preoptic area, and the ambient temperature at which maximal amounts of REM sleep occurred frequently shifted from 30 to 25°C. During the first postlesion month, amounts of slow wave sleep, REM sleep and total sleep time (TST), and the proportion of time spent in REM sleep to TST all improved significantly at the ambient temperatures at which the most REM sleep occurred (high REM temperatures). In contrast, at the ambient temperatures at which the least

REM sleep occurred, these variables were as depressed one month after preoptic lesions as they were at 5 days postlesion. REM sleep bout length was severely shortened after forebrain damage, and this was the only sleep disturbance not attenuated at high REM sleep temperatures. After smaller lesions, initial deficits were less severe and normal amounts of sleep returned earlier. However, as was the case for large lesions, sleep deficits were most severe and persistent at low REM sleep temperatures. Thus, the amount, severity and duration of the deficits in sleep after basal forebrain lesions are highly dependent on the ambient temperature at which the rats are tested.

In a third set of experiments, we examined the behavioral responses of newborn rabbits to pyrogen-induced fevers. We found that normal 1-3 day old rabbit pups did not develop a fever reflexively to a dose of pyrogen that caused adult rabbits to become febrile. However, the pups became febrile by choosing to stay in a warm part of a thermally graded alleyway. At much higher doses normal pups were able to develop a fever reflexively as well as behaviorally. However, pups that were neglected by their mothers only became febrile in the alleyway.

In attempting to determine the mechanism of maternal neglect we found that starvation for two days and a chronic mild cold stress prevented the rises in body temperature that normally occur in newborn pups. Nevertheless, the stressed pups selected significantly warmer positions in the thermal gradient than did saline-injected controls and thereby raised their body temperatures. Enhanced heat seeking and subsequent fever were also observed in normally fed pups that were incubated at 24^{0}C and had become hypothermic after pyrogen injection. The responses of the pups before they were allowed to thermoregulate behaviorally resemble the types of thermal responses to infection seen in human newborns. The temperature selection of these pups, and others, indicates that pyrogen elevates the set points of newborn rabbits when endothermic fever is attenuated or even absent.

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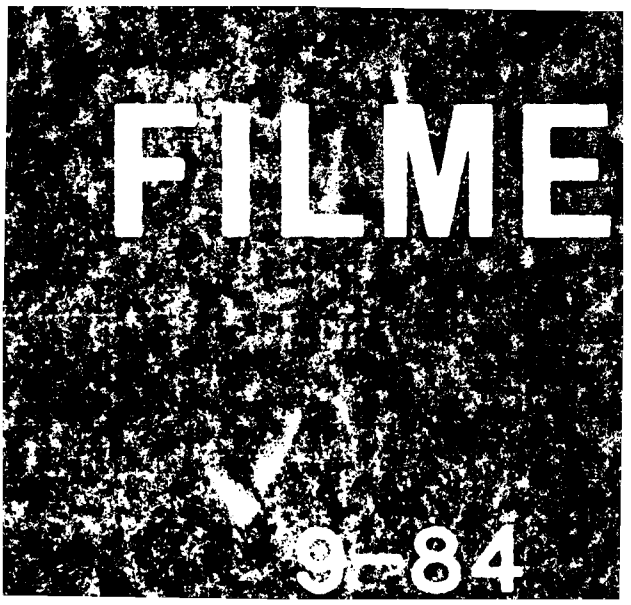
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